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## Review Article

# Effect of high intake of heavy metals from environmental air and in food in diabetic patients

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**Abstract**

Diabetes mellitus is an endocrine disorder and affecting millions of people. It remains latent and its secondary obstacles leads to the mortality and morbidity. Various metal such as arsenic, beryllium, cadmium and nickel have been linked with the occurrence of diabetes mellitus in peoples exposed to these elements. Some elements like iron and copper are crucial minerals that are necessary for a variety of molecules to maintain their normal structures, functions of cells to existence, grow, and multiply. The homeostasis of iron and copper is coordinated regulation by different proteins concerned in uptake, excretion and intracellular storage or transferring. This study connected airborne levels of these metals with diabetes mortality. The lowest air levels detected were beryllium and cadmium, with nickel showing the highest levels. This supported diabetes mortality effects of air pollution and correlating arsenic, beryllium, cadmium and nickel with diabetes incidence. Although iron is essential but it can be toxic in high amounts. Iron is a transit mineral can generate various reactive oxygen or nitrogen species so abnormal metabolism of iron can lead to numerous chronic pathogenesis. Oxidative stress is one of the main contributing factors for diabetes and diabetic problems. Iron overload may increases risks of insulin resistance and diabetes.

## 1. Introduction

Diabetes mellitus is an endocrine disorder, affecting millions of individuals. It is a key cause of morbidity in the developed countries. The WHO reported that about 300 million individuals will have diabetes mellitus by the year 2025 [1]. It affects people of all ages and ethnic groups [2]. Diabetes influences about 5% of the world population and treatment of diabetes without any side effects is still a challenge to the medical system [3]. Diabetes is a heterogeneous group of disorders that lead to rise of glucose level in the blood. Chronic hyperglycemia and risk of the producing problems are the two joint properties which have held the concept of diabetes together. Trace elements roles mainly as catalysts in enzyme systems; some metallic ions, like iron and copper, contribute in oxidation-reduction reaction in energy metabolisms. Iron, as a part of hemoglobin and myoglobin and plays a crucial role in the transport of oxygen. All trace elements are toxic if consumed at adequately high amounts for long times. The distinction between toxic intakes and optimal intakes for essential trace elements is great for some elements but is much smaller for others. Trace elements are also present in food in organic and inorganic form. In human body only 5% of body weight is mineral matter, vital to all mental and physical processes and for well-being. They are very important factors in keeping all physiological activities, are constituents of the teeth, bones, tissues, muscle, blood and nerve cells. They may act as catalysts for various biological reactions within the body, they are crucial for transmission of messages through the central nervous system, digestion and metabolism or utilization of all nutrients in foods. Micronutrients, minerals and trace elements are very important for the human body. They have various roles in metabolism and body functions. They are essential for the proper function of cells, tissues, and organs. Some minerals, such as iron, make up part of many proteins and enzymes in the body. Minerals also play a role in the building up of muscle and bone and are important for normal body growth. It is well established that several trace elements are of great importance in a number of biological processes, mostly through their action as activators or inhibitors of enzymatic reactions, by competing with other elements and proteins for binding sites, by influencing the permeability of cell membranes, or through other mechanisms. It is therefore reasonable to assume that these minerals would also exert an action, either directly, or indirectly, on the pancreas. Disorders of mineral metabolism are sometimes passed from parents to their children through genes. Other medical conditions, such as starvation, diarrohea, or alcoholism, can cause mineral metabolism problems.

The association between environmental heavy exposure and different chronic diseases like depression, hypertension and cardiovascular diseases [4]. Heavy metals have no biological or nutritional value. However, one regular topic is the relationship between heavy metal exposure and the progress of diabetes mellitus[5-19], an effect that might involve direct cytotoxicity or autoimmunity [20]. The effects on diabetes might also impact renal disease by these metals, particularly cadmium [15]. Diabetes mellitus is a disease connected with demographic factors such as socioeconomic status and race. It is necessary to elucidate the consequences of heavy metal exposure at the population level to the prevalence and mortality of diabetes [9-12]. The associations between environmental contaminates and diabetes mellitus. The arsenic and cadmium levels were higher in diabetic subjects than age-matched non-diabetic controls in hair, blood and urine [5]. Similarly, adverse effects on pancreatic islet cells from arsenic and cadmium [6]. Higher rates of diabetes mellitus in populations exposed to high levels of arsenic in drinking water [9,10]. Inadequate evidence to support arsenic as playing a causal role in diabetes [12], Some other studies have supported this hypothesis [7-12]. The evidence linking beryllium to diabetes is likely via this element's ability to induce an autoimmune T-cell response, ultimately attacking islet cells and other organs [17,18]. In fact, beryllium up-regulates programmed death-1 expression on beryllium-Specific CD4+T Cells, a pathway leading to the onset of diabetes [19,20]. Arsenic, cadmium has been linked to diabetes mellitus [5,6]. A report demonstrated a

relationship between high urinary levels of cadmium with impaired glucose tolerance [14]. The evidence supporting the link between cadmium exposure and diabetes, finding that cadmium reduces insulin levels, is directly cytotoxic on the pancreas and may be a factor in development of this disease [15]. Potentially connecting cadmium to diabetes mortality, cadmium is likely toxic to nerve terminals, and thus may exacerbate complications from this disease[16]. The nickel effect on diabetes mellitus has bit inconsistent. Nickel is known to avert the development of streptozotocin-induced diabetes in rats and preventing hyperglycemia [21,22]. Additionally, no relationship between nickel blood levels and diabetes in humans [23,24]. By contrast, in concert with nitric oxide, nickel can induce hyperglycemia in rats [8].

Minerals and trace elements may exert protective or scavenging effects, as well as being essential components of several key enzymes in intracellular antioxidant defense [25]. Their deficiency, or excess, may contribute to derangement of the pro-oxidant/anti-oxidant balance, and hence to the progressive appearance of secondary complications as the disease advances. Both type I and II diabetes are accompanied by alterations in micronutrient absorption, tissue uptake, and excretion, some in a time-dependent fashion. A major effect of these changes may be a worsening of the oxidative balance, with declining capability to combat endogenously produced free radicals. Macro and microelements are involved in the complex processes of development of the secondary complications of diabetes mellitus affecting many organs. They may be integral components of antioxidant enzymes (e.g., Cu, in case of superoxide dismutase, and Se for Glutathione peroxidase), cofactors in a variety of enzymatic processes of importance in glucose and lipid metabolism (e.g., Cu), or potential pro-oxidant catalysts (e.g., Cu, Fe). The etiology of diabetes and its complications still is not clear, however several factors as aging, obesity and oxidative damage have been implicated. Several micronutrients have beneficial effects in healthy subjects and also in diabetes [26,27]. Copper, iron and manganese are important components of metalloenzymes such as Se–cys containing glutathione peroxidase, Cu/Fe cytochrome C oxidase and/or different types of superoxide dismutases, all of them imperative in intra- and extra-cellular antioxidant defense [28]. Copper is found in the liver, gallbladder, lungs and heart. It is essential primarily for the absorption and metabolism of iron. A deficiency in copper results in the same effects as an iron deficiency, such as retarded hemoglobin production, general debility, limited growth, etc. Some sources have estimated about 2 milligrams per day. Very few cases of copper depletion have been observed in humans. Copper is needed for synthesis of hemoglobin, proper iron metabolism, and maintenance of blood vessels. Copper is an integral part of the enzyme copper-zinc superoxide dismutase (CuZn SOD); also present in other enzymes, including cytochrome oxidase, ascorbic acid oxidase, and tyrosinases. It is usually found in the red blood cells, and in blood plasma. The chief supplementary sources of copper are seafood, nuts, legumes, green leafy vegetables. Insufficient copper has been associated with: changes in hair colour & texture, and hair loss; disturbances to the nervous system; bone diseases. Serious deficiency is rare but can lead to: Menke's syndrome.

Copper has been shown to be elevated in experimentally diabetic rats [29]. Iron status is little affected by diabetes per se; however, because of its role as a catalyst in free radical generation, and the given state of increased oxidant stress in diabetes, it is probably advisable for diabetic individuals to avoid excess iron. Hence, this present research is mainly focused on the role of the following essential trace elements in Type I DM and Type II Diabetes mellitus conditions: iron, selenium, copper, chromium, vanadium and molybdenum. Interactions between these trace elements and hyperglycemia are also briefly considered. Epidemiologic data on the relationship between many of the trace elements and the incidence of diabetes and hypertension are incomplete. Most such studies have focused on cadmium, chromium, and selenium. Furthermore, most of the evidence is not related to dietary exposure but focuses, for example, on inhalation exposure in the workplace. The biochemical role for copper is primarily catalytic, with many copper metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. Many copper metalloenzymes have been identified in humans [30]. Ferroxidases are copper enzymes found in plasma, with a function in ferrous iron oxidation ($Fe^{2+} \rightarrow Fe^{3+}$) that is needed to achieve iron's binding to transferring [31]. Ferroxidase I, also called ceruloplasmin, is the predominant copper protein in plasma and may also have antioxidant functions. Defects in ceruloplasmin function produce cellular iron accumulation, a result that supports its ferroxidase role [30]. Ferroxidase II is found in human plasma, but it may have a role in iron metabolism in specific cellular sites. A transmembrane copper-containing protein (hephaestin) with ferroxidase activity has been described [32]. Cytochrome c oxidase is a multisubunit enzyme in mitochondria that catalyzes reduction of $O_2$ to $H_2O$. This establishes a high energy proton gradient required for adenosine triphosphate (ATP) synthesis. This copper enzyme is particularly abundant in tissues of greatest metabolic activity including heart, brain, and liver. Dopamine β monooxygenase uses ascorbate, copper, and $O_2$ to convert dopamine to norepinephrine, a neurotransmitter, produced in neuronal and adrenal gland cells. Dopa, a precursor of dopamine, and metabolites used in melanin formation are oxidatively produced from tyrosine by the copper enzyme tyrosinase. α-amidating monooxygenase , also called peptidylglycine alpha amidating monooxygenase, uses copper and ascorbate to remove two carbons from a C-terminal glycine of peptides, thus generating an amide. Several peptide hormones are posttranslationally modified by alpha amidating monooxygenase. Copper/zinc superoxide dismutase (Cu/Zn SOD) uses two copper atoms for the conversion of the superoxide anion ($O_2^-$) to $H_2O_2$ and $O_2$. Zinc atoms have a structural role in the enzyme [30]. The enzyme is localized in the cytosol and, along with the mitochondrial manganese-containing form, provides a defense against oxidative damage from superoxide radicals that, if uncontrolled, can lead to other damaging reactive oxygen species. Mutations in the Cu/Zn SOD gene, which alter the protein's redox behavior, produce amyotrophic lateral sclerosis. These are the principal copper metalloenzymes found in humans. There is substantial documentation from animal studies that diets low in copper reduce the activities of many of these copper metalloenzymes. Activities of some copper metalloenzymes have been shown to decrease in human copper depletion [33]. Physiologic consequences resulting from copper deficiency include defects in connective tissue that lead to vascular and skeletal problems, anemia associated with defective iron utilization, and possibly specific aspects of central nervous system dysfunction [30]. The immune and cardiac dysfunction occurs in experimental copper deficiency and the development of such signs of deficiency has been demonstrated in infants [35]. Iron plays a pathogenic role in diabetes and its complications such as microangiopathy and atherosclerosis[36]. The importance of protein glycation is well known in the pathogenesis of diabetic vascular complications. Transition metals also play a role in protein glycation induced by hyperglycemia. Glycated proteins possess a substantial attraction for the transition metals, and the bound metal retains redox activity and contributes to catalytic oxidation processes [37]. Thus, should similar glycochelates form in vivo, reactions mediated by the iron chelates could be involved in the vascular complications of diabetes [38]. During superoxide-dependent formation, more reactive radicals such as hydroxyl radical (OH•) requires the presence of transition metal ions such as copper or iron [39]. Although OH• is highly reactive, it's *in vivo* formation is contingent upon the availability of physiological iron. Interestingly, in the present study, a parallel increase in the amount of iron with the malondialdehyde release (index of oxidative stress) was observed in Type I and Type II diabetic patients as compared to healthy normal individuals.

 

Since iron is a reactive metal ion that is known to catalyze damage to cellular macromolecules caused by oxygen radicals, its reduction from $Fe^{3+}$ to the $Fe^{2+}$ state plays a major role in lipid peroxidation process. As the concentration of iron increases, it finally accumulates in the liver. Ferritin, an iron storage protein may function as a source of iron for promotion of superoxide-dependent lipid peroxidation [39]. The small size of $O_2$-, which is generated by xanthine oxidase in conjunction with its ability to reduce chelated iron, suggests that it is an excellent candidate for the mobilization of iron from ferritin. All parenterally administered iron in excess of the ferritin storage mechanism accumulates in the liver as hemosiderin. Thus the rise in the amount of iron in the serum of the diabetic patients might be either due to increased release of iron from the body storage depot into the systemic circulation or to attenuation in the process of storage related to oxidative stress. Evidence linking iron to diabetic nephropathy includes

*1*) Animal and epidemiological investigations,

*2*) Researches in which an increased amount of iron has been demonstrated in the kidneys of both animals **[**40,41**]** and humans**[**42] with kidney disease,

*3*) Evidence for higher urinary iron in patients with diabetic nephropathy, and

*4*) The inhibition of progression either by an iron-deficient diet or agents that bind and eleminate iron (chelators) **[**43-45].

Earlier experimental investigations offer extensive proof for the role of iron and oxidants in the pathogenesis of diabetic nephropathy [46-50]. Oxidative stress from factors such as hyperglycemia, advanced glycation end products, and dyslipidemia contribute to the obtainability of intracellular iron that can produce and viciously worsen oxidative deterioration and renal damage. Iron content in the kidney has been demonstrated to be amplified in an animal model of diabetes [51], and urinary iron excretion is elevated early in the course of diabetic renal disease in humans **[**50,52]. There is substantial proof that, once renal insufficiency progresses, irrespective of etiology, it inclines to headway over time. This has been interpreted to show certain common pathways for development of kidney disorders. Most notably, the pathogenic part of iron in progression is indicated by the observation that development can be prohibited either by an iron-deficient diet or chelators **[**43-45]. A current randomized trial involving 191 patients with diabetes, proteinuria, and a decreased glomerular filtration rate exhibited that a low-iron–available, carbohydrate-restricted, polyphenol-enriched diet compared with a standard protein-restricted diet had a renoprotective activity **[**53**]**. Epidemiologic investigations [54-56] in explicit iron overload states such as transfusional iron overload and hemochromatosis have indicated that the incidence of coronary heart disease is increased [57] and that dietary intake with iron chelation recovers cardiovascular outcome. Likewise, numerous researches have indicated a direct connotation between higher iron intake, body iron reservoirs, and cardiovascular jeopardy in the general population. Elevated intake of heme iron is related with augmented cardiovascular events [58-61], and increased body iron stores are linked with myocardial ischemia in a prospective epidemiological investigation [62]. Reliable and sensitive methods need to be developed to precisely measure the free/catalytic iron that participates in oxidative injury. Iron chelation therapy may present a novel way to interrupt the cycle of catalytic iron–induced oxidative stress and tissue injury and consequent release of catalytic iron in diabetes and to prevent diabetes-related complications.

Copper has been known to be essential for health for more than three quarters of a century. Copper functions as a component of a number of metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. The primary criterion used for copper is a combination of indicators, including plasma copper and ceruloplasmin concentrations, erythrocyte superoxide dismutase activity, and platelet copper concentration in controlled human depletion/repletion studies [63]. There was a significant elevation observed in serum copper content in Type I and Type II diabetic patients as compared to normal controls. There is a significant increase in the levels of copper in type 1 DM subjects when compared to healthy control subjects. There is significant increase in the levels of copper in type 2 DM subjects when compared to healthy control subjects. There is significant increase in the levels of copper in type 1 DM subjects when compared to type 2 DM subjects. Elevated level of copper in type I and type II diabetes mellitus is a major risk factor for the incidence of cardiovascular disease [64]. Diabetic patients with vascular complications have higher plasma copper levels than diabetic patients without complications or normal controls [64]. Patients with the “metabolic syndrome” (patients having common risk factors such as obesity, hypertension, glucose intolerance, and dyslipidemia) also have elevated copper levels [65]. Copper overload in diabetes mellitus differs from that in Wilson's disease through differences in their respective causative molecular mechanisms, and resulting differences in tissue localization and behaviour of the excess copper. Pathogenetic tissue binding of copper is elevated in diabetes. It may well be mediated by advanced-glycation end product (AGE) modification of susceptible amino-acid residues in long-lived fibrous proteins, for example, connective tissue collagens in locations such as blood vessel walls. The copper metabolism becomes abnormal after induction of diabetes in rats and that the copper chelator trientine, given to these animals, alleviated their heart failure, improved cardiomyocyte structure, and reversed elevations in left ventricular collagen and β1 integrin without lowering blood glucose. In diabetic patients, trientine therapy decreased left ventricular hypertrophy [63], the beneficial effects of trientine in animal studies of diabetic neuropathy [66]. The elevated serum ceruloplasmin levels are associated with albuminuria in Korean men with type 2 diabetes mellitus [67].

Reactive oxygen species (ROS) are induced under diabetic conditions and are likely associated with the development of diabetes. It is also known that ROS production is facilitated in the presence of copper ion through the Fenton reaction **[**68]. Thethe involvement of copper ion in the pathogenesis of type 2 diabetes and evaluated the potential usefulness of a copper chelating agent for the treatment of type 2 diabetes **[**58**]**. Since copper ion is involved in the development of diabetes, it may be a potential therapeutic target for diabetes. The biochemical role for copper is primarily catalytic, with many copper metalloenzymes acting as oxidases to achieve the reduction of molecular oxygen. Many copper metalloenzymes have been identified in humans [69]. Copper/zinc superoxide dismutase (Cu/Zn SOD) uses two copper atoms for conversion of the superoxide anion ($O_2^-$) to $H_2O_2$ and $O_2$. Our results also confirmed same pattern and showed significant enhancement in lipid peroxidation level (malondialdehyde release) in diabetic conditions. A concomitant decline in antioxidant status (FRAP assay) was also observed. Several other clinical observations deserve further investigation, but there is insufficient evidence to link them to marginal copper status. Glucose tolerance was lower in two of a group of eight men consuming 80 μg/day of copper than in men consuming higher levels of copper [70], but similar observations have not been reported at lower intakes of copper in other studies.

## 2. Discussion

This study has found an association between heavy metals arsenic, beryllium, cadmium and nickel air contaminants and age adjusted diabetes mellitus mortality rates. Although associations between these heavy metals arsenic, beryllium, cadmium and nickel and diabetes prevalence by the high concentrations of these heavy metals in the diabetic patient and increase in diabetes mortality. Hazardous air pollutants-including arsenic, beryllium, cadmium and nickel-an analysis of these elements’ concentrations based might start to mitigate diabetes death for pollutants [70,71]. It is important to note that these results are subject to a number of limitations. First, although this study con- trolled for many county-level risk factors for

 

diabetes, it could not control for other confounders. Such factors might include county level obesity and heart disease rates. Additionally this analysis was unable to control for other environmental toxins known to be associated with diabetes (e.g., chromium), nor is it known the sources from which these toxins are released. In addition, since ecological studies compare data at the population level, these results cannot be extrapolated down to the individual level. For example, it could be that no person with diabetes who died in a specific county was ever exposed to these elevated environmental toxins. In spite of the great amount of work that has been done on the relationships between trace elements and diabetes, the evidence is still fragmentary. The nature of the correlations—whether it is a cause-to-effect relationship or simply a statistical association—is still unknown. The mechanisms of action are also poorly understood. Further clinical investigations are needed to elucidate these problems, and hence the present study has been taken as a contribution to the research activities in this field with special emphasize on role of minerals in influencing the metabolic homeostasis in Type I and Type II diabetes [71].

## 3. Conclusion

There is suggestive evidence that iron and copper plays a pathogenic role in diabetes and its complications such as microangiopathy and atherosclerosis. Reliable and sensitive methods need to be developed to precisely measure the free/catalytic iron and copper that participates in oxidative injury. Hence measuring the levels of iron and copper in early age may help to predict the onset of diabetes and its secondary complications which may postpone the diabetes.

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